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Updates in the Management of Peripheral Arterial Disease: Focus on Reduction of Atherothrombotic Risk

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KEY TAKEAWAYS

- Peripheral arterial disease (PAD) is an underdiagnosed atherosclerotic disease, usually affecting arteries in the lower extremities, with possible thromboembolic complications.
- Diagnosis of PAD involves taking a history with focus on claudication symptoms and applicable risk factors as well as a physical exam for signs of arterial insufficiency; diagnosis is confirmed with testing, usually a resting ankle-brachial index.
- Comprehensive management should include exercise and smoking cessation, as well as addressing comorbidities, such as hyperlipidemia, hypertension, and diabetes.
- Treatment approaches for reducing atherothrombotic risk in PAD include antiplatelet agents, anticoagulants, and surgical interventions.
- Treatment with rivaroxaban plus aspirin in

patients with PAD at low risk of bleeding should be considered for prevention of cardiovascular and major limb adverse events.

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INTRODUCTION

Peripheral arterial disease (PAD) is a type of atherosclerotic disease that leads to partial or complete peripheral artery

occlusion, resulting in reduced blood flow and ischemia.¹ PAD can affect lower- or upper-extremity arteries, but lower extremity sequelae are more commonly observed and tend

to be the focus for diagnosis and treatment of the disease. PAD can present with symptoms of intermittent claudication—pain in the legs, primarily the calves—that worsens with walking and resolves with rest. However, > 50% of patients with PAD may present without symptoms.² Complications of PAD can include ulcers, gangrene, limb ischemia, myocardial infarction (MI), stroke, and death; patients who have more risk factors have an increased risk of these complications.³ PAD also has a strong association with cardiovascular (CV) and cerebrovascular disease and related complications due to the systemic nature of atherosclerosis.^{4,5} Historically, PAD has been an underdiagnosed and undertreated disease, but increased focus in recent years has prompted development of society guidelines and other clinical evidence supporting proper evaluation and pharmacologic treatment of PAD.^{3,6,7}

CASE SCENARIO

TF is a 62-year-old man who presents to your clinic with continued complaints of leg pain he believes is due to his statin drug; he would like to stop taking it. The pain has been going on for the past 3 months, and the patient has been taking atorvastatin for 5 years. Upon further evaluation and questioning, you determine that his leg pain only occurs when he is walking and resolves upon rest.

Past medical history: hypertension, hyperlipidemia, type 2 diabetes (T2D)

Family history: father had coronary artery disease and died of a stroke at age 66; mother is alive with T2D

Social history: former smoker, no alcohol use

Lab work and vitals: glycosylated hemoglobin (A1c) 7.1%, blood pressure 128/74 mm Hg in clinic today

Current medications: metformin 1000 mg twice daily, atorvastatin 40 mg daily, lisinopril/hydrochlorothiazide (HCTZ) 20/25 mg daily

Epidemiology

In this patient, the most immediate concern would be an increased risk of atherothrombotic CV events and limb ischemia—patients with symptomatic PAD have a 70% increased risk for subsequent CV events, and critical limb ischemia is reported in up to 29% of patients with PAD.^{5,8,9} In the United States, approximately 8 to 12 million adults aged ≥ 40 years are affected by PAD, and > 200 million individuals are affected worldwide.^{2,7} The prevalence of PAD increases with age, and disease distribution between men and women is fairly similar.^{2,7} The rate of disease in African Americans is twice that of non-Hispanic whites, and Hispanic and Chinese individuals

are about 55% less likely than non-Hispanic whites to have PAD.¹⁰ About 20% to 30% of people with PAD have diabetes, a major risk factor for PAD, and smokers are 2.5 times more likely to develop PAD.^{11,12} In symptomatic patients, the femoral and popliteal arteries are affected up to 90% of the time.¹³ Rates of amputation due to PAD vary by geographic region in the United States, and the overall amputation risk is 3% to 4%.¹⁴

Unmet Needs in PAD

The Reduction of Atherothrombosis for Continued Health (REACH) Registry is a compilation of over 67,000 patients aged ≥ 45 years in 44 countries between 2003 and 2004. Each patient had established arterial disease (8273 patients with PAD) or ≥ 3 risk factors for atherothrombosis.¹⁵ One key finding from the registry is that despite clear guideline recommendations and frequent implementation of appropriate therapy, the risk of CV events remains high.

Patients with PAD are at high risk for major adverse cardiovascular events (MACE) and major adverse limb events (MALE), despite use of antiplatelet therapies, anticoagulants, and revascularization.¹⁶ Additionally, functional status can be severely limited by occurrence of claudication and inadequate resolution of limb ischemia, as well as bleeding adverse events from antiplatelet or anticoagulant therapies. There is a need for PAD therapies that address these issues and that have acceptable patient safety and tolerability.

Atherothrombotic events often lead to complications of PAD, such as limb ischemia and CV events. In fact, thrombophilic factors often influence the progression of chronic PAD to critical limb ischemia.¹⁷ Polyvascular disease, ie, atherosclerosis in multiple anatomic locations, is common in patients with PAD and is associated with an increased rate of thrombotic events as well as other CV outcomes, such as MI or stroke. Thus, there is a need for detection and medical treatment of polyvascular disease in addition to PAD.¹⁸

CLINICAL ASSESSMENT

History and Physical Examination

Patients at risk of PAD should undergo a thorough medical history, review of symptoms, and physical examination. Notably, the symptoms of PAD can be variable; some patients will exhibit characteristic claudication symptoms, but most patients are asymptomatic or present with advanced (critical limb ischemia) or atypical leg symptoms.¹⁹ A vascular examination for PAD should include inspection of the legs and feet for varicosities, pigmentation, dryness, and turgor; auscultation for femoral bruits; and palpation and assessment of lower extremity pulses.²⁰

Risk factors for PAD are similar to those for other atherosclerotic diseases (**TABLE 1**).^{21,22} The 2016 American Col-

lege of Cardiology (ACC) and American Heart Association (AHA) guidelines for management of lower extremity PAD identify 4 patient groups at risk for PAD, accounting for age and other risk factors.³ Notably, erectile dysfunction (ED) is common among patients with PAD, and patients presenting with ED may need to be screened for PAD.²³ After investigating the history and physical symptoms for a patient at risk for PAD, the diagnosis of PAD should be confirmed with diagnostic testing. This would be a suggested approach for the case scenario provided above.

Diagnostic Testing

The 2016 ACC/AHA guidelines for management of lower extremity PAD suggest an algorithm to aid clinicians in using a systematic approach to diagnostic testing for PAD (FIGURE). The core diagnostic test, and the only one required to establish a diagnosis of PAD, is the resting ankle-brachial index (ABI).³ The resting ABI measurements are obtained using a Doppler device by checking systolic blood pressure at the brachial artery and comparing it to systolic blood pressure at either the dorsalis pedis or posterior tibial arteries.²⁴ These blood pressures should be checked in a supine position, and the ABI is calculated by dividing the higher lower extremity pressure (dorsalis pedis or posterior tibial) by the higher of the left or right arm pressure.

Physiologic tests, such as exercise treadmill ABI testing and toe-brachial index (TBI), may be helpful with certain clinical presentations where a resting ABI does not provide a clear diagnosis (FIGURE).²⁵ Exercise ABI is helpful for identifying PAD in patients with a normal ABI but continued exertional leg pain.²⁶ The TBI can be used for patients with noncompressible arteries (ABI > 1.40) and, if abnormal, can establish a diagnosis of PAD.

Patients who experience persistent and bothersome claudication symptoms despite guideline directed management and therapy (GDMT) for PAD may be considered for revascularization.³ Potential imaging modalities to determine eligibility for revascularization include magnetic resonance angiography (MRA), computed tomography angiography (CTA), duplex ultrasound, and invasive angiography.

Screening

According to the US Preventive Services Task Force (USPSTF), there is insufficient evidence to recommend for or against use of the ABI to screen for PAD in asymptomatic adults.²⁷ This is primarily due to the lack of studies evaluating the benefits and harms of screening with ABI. However, the ABI is still recognized in this USPSTF statement as a more accurate method to identify PAD than history and physical exam alone.

As mentioned previously, patients with PAD are at risk for atherosclerosis in arteries outside the lower extremities,

including the carotid, vertebral, renal, and mesenteric arteries as well as the upper extremity blood vessels.²⁸ To identify disease in vascular beds other than the lower extremities, elucidation of symptoms associated with these areas could be helpful. For example, upper extremity exertional pain might indicate atherosclerotic disease in the upper extremities, and history of hypertension or renal failure may suggest renal atherosclerotic disease.²⁸ However, there is no evidence that screening other vascular beds for asymptomatic atherosclerosis in patients with PAD improves clinical outcomes.³ Rather, addressing the risk of complications from PAD through GDMT is a recommended approach.

TREATMENT

CASE SCENARIO (CONTINUED)

TF presents to your clinic a few years later following revascularization for acute limb ischemia (ALI) due to complications from PAD.

Past medical history: hypertension, hyperlipidemia, T2D, PAD

Family history: father had coronary artery disease and died of a stroke at age 66; mother is alive with T2D

Social history: former smoker, no alcohol use

Labs and vitals: A1c 7.3%, blood pressure 134/70 mm Hg in clinic today

Current medications: metformin 1000 mg twice daily, atorvastatin 40 mg daily, lisinopril/HCTZ 20/25 mg daily, aspirin 81 mg daily

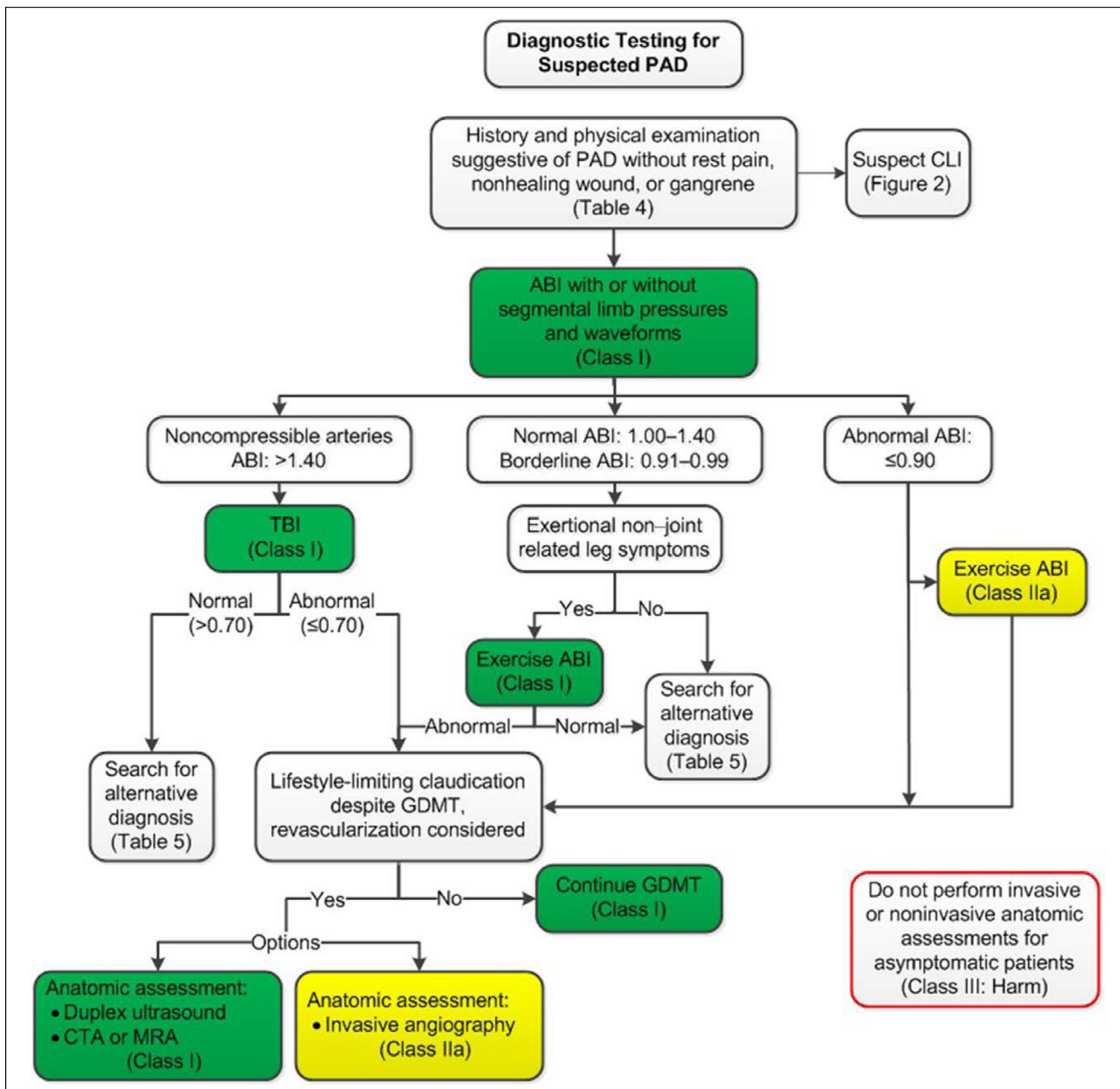
Comprehensive Therapy

Approaches to treatment of patients with PAD should involve a holistic approach, considering patients' individual risk factors and preferences. In general, lifestyle modification and structured exercise are helpful for improving functional sta-

TABLE 1. Risk Factors for PAD^{3,21,22}

Risk factors that correlate with the 4 ACC/AHA patient groups at risk for PAD
Age ≥ 50 years
Diabetes
History of smoking
Hyperlipidemia
Hypertension
Obesity
Family history of PAD
Known atherosclerosis in another vascular bed
Decreased kidney function
Non-Hispanic Black ethnicity

FIGURE. **Diagnostic Testing for Suspected PAD**



CLI, critical limb ischemia.

Source: 2016 ACC/AHA Guidelines for Management of Lower Extremity Peripheral Artery Disease. Republished with permission of the American College of Cardiology, from Gerhard-Herman MD, et al. *J Am Coll Cardiol.* 2017;69(11):e71-e126. Permission conveyed through Copyright Clearance Center, Inc. References within this Figure to Figure 2 and Tables 4 and 5 pertain to items in the original publication.

tus and reducing CV events.³ Comorbidities such as hyperlipidemia, hypertension, diabetes, and smoking status should also be addressed as part of reducing CV risk. Smoking cessation is essential for patients with PAD. Patient-centered care should also take into consideration the patient’s perspective with shared decision-making as treatments are discussed.

Pharmacotherapy

Current pharmacotherapy recommendations for PAD are informed by several clinical guidelines, and treatment goals encompass CV and thrombotic risk reduction, management and prevention of ALI, and improvement in functional symptoms.^{3,29-31} Of note, the most recent clinical guideline from the

American Diabetes Association in early 2021 is endorsed by the ACC and suggests therapies for atherothrombotic risk reduction in patients with diabetes and elevated CV risk²⁹:

- Antiplatelet agents are recommended to reduce stroke, MI, and vascular death in patients with symptomatic PAD.³
- Combination treatment with aspirin and low-dose rivaroxaban for prevention of CV events and MALE should be considered for patients with PAD and/or stable coronary artery disease.^{29,30}
- Statin therapy is indicated for all patients with PAD, due to its designation as a subtype of atherosclerotic cardiovascular disease (ASCVD) and benefit for CV outcomes.^{32,33}
- In patients with PAD and hypertension, antihypertensive therapy is suggested to reduce the risk of stroke, MI, heart failure, and CV death.³
- Following revascularization post-ALI, antiplatelet drugs and statins are recommended to decrease CV complications.³¹ Rivaroxaban plus aspirin may also be an option for decreasing amputations and mortality after revascularization.^{31,34}
- Cilostazol is effective for increasing walking distance and alleviating leg pain symptoms in patients with claudication but is often associated with adverse effects, including headache, dizziness, palpitations, and diarrhea.³ Notably, pentoxifylline is not recommended as a treatment for claudication due to lack of efficacy.³

In the case scenario, patient TF is appropriately receiving high-intensity statin therapy and antiplatelet therapy (aspirin 81 mg daily). To reduce the risk of MACE and MALE, rivaroxaban 2.5 mg twice daily might be added to the patient's regimen, or a more potent antiplatelet agent, such as clopidogrel or vorapaxar, could be added to reduce MACE and limb ischemia.

US Food and Drug Administration (FDA)-Approved Drugs for PAD That Reduce Thrombotic Risk

Several prescription-only drugs have FDA approval supporting their use in reducing thrombotic risk in PAD. Clopidogrel is labeled for the treatment of established PAD, as well as recent MI and recent stroke.³⁵ It is a potent P2Y₁₂ inhibitor, reducing platelet activation and aggregation, and is demonstrated to reduce the rate of new MI, new ischemic stroke, and other vascular death. Clopidogrel is administered as a 75-mg tablet once daily for PAD. Rivaroxaban selectively inhibits factor Xa, decreasing thrombin generation. It also inhibits thrombin-induced platelet aggregation.³⁶ Rivaroxaban is indicated for PAD (and coronary artery disease) to reduce the risk of MACE. For PAD, rivaroxaban is administered as

2.5 mg twice daily along with 75–100 mg aspirin once daily to reduce the risk of major thrombotic vascular events, including after recent lower extremity revascularization. Vorapaxar is a protease-activated receptor-1 (PAR-1) antagonist, inhibiting thrombin-induced platelet aggregation, that is indicated for use in patients with PAD or history of MI to reduce thrombotic CV events.³⁷ It has demonstrated a reduction in rates of a combined endpoint that included CV death, stroke, MI, and urgent coronary revascularization.

A review of the evidence informing guideline recommendations and drug labeling can assist clinicians with identifying patients who may benefit from particular therapies (TABLE 2).

Aspirin vs clopidogrel. The CAPRIE study investigated aspirin vs clopidogrel in patients with symptomatic atherosclerotic vascular disease, including PAD.³⁸ Over a mean follow-up of 1.91 years, patients receiving clopidogrel experienced a reduction of 8.7% in the combined risk of ischemic stroke, MI, or vascular death ($P = .043$). The annual risk rates for the composite endpoints were 5.32% and 5.83% for clopidogrel and aspirin, respectively. Gastrointestinal hemorrhage was more common in patients taking aspirin (2.66%) than clopidogrel (1.99%; $P < .002$).

Aspirin with or without clopidogrel. Clopidogrel with aspirin was compared to aspirin alone for patients with clinical CV disease (inclusive of PAD) or multiple CV risk factors in the CHARISMA trial.³⁹ The composite primary endpoint included stroke, MI, or CV death. Overall, the rate of the composite endpoint was lower for patients taking clopidogrel with aspirin compared to patients taking aspirin alone (6.8% vs 7.3% respectively), but this was not statistically significant. Further, patients with multiple risk factors had higher (but not statistically significant) rates of the composite endpoint when treated with clopidogrel with aspirin. However, significant reductions in risk were observed with clopidogrel and aspirin when hospitalizations for ischemic events were included in the endpoint and for patients with clinically evident atherothrombosis. In a post-hoc analysis of CHARISMA that evaluated the subset of patients with PAD, clopidogrel plus aspirin reduced rates of MI and hospitalization for ischemic events with an increase in minor bleeding compared to aspirin alone.⁴⁰

The CASCADE trial assessed the addition of clopidogrel to aspirin after coronary artery bypass grafting.⁴¹ Participants were randomized to receive either aspirin 162 mg plus clopidogrel 75 mg daily or aspirin 162 mg plus placebo daily for 1 year. At 1 year, the mean intimal area was slightly lower in the clopidogrel-plus-aspirin group compared to aspirin alone ($4.1 \pm 2.0 \text{ mm}^2$ vs $4.5 \pm 2.1 \text{ mm}^2$), but this was not statistically significant. No differences in adverse effects were identified.

The use of aspirin in patients < 50 years of age is not rec-

TABLE 2. Prescription Drugs Studied for Prevention of Atherothrombotic Events in PAD

Drug	Key Trials	Outcomes	Safety
Clopidogrel	CAPRIE ³⁸ CHARISMA ^{39,40}	<ul style="list-style-type: none"> Significant reduction of stroke, MI, or vascular death compared to aspirin. Reduced rates of MI and hospitalization for ischemic events when added to aspirin. 	Observed lower rates of gastrointestinal hemorrhage than aspirin, but increase in minor bleeding.
Ticagrelor	EUCLID ¹²	<ul style="list-style-type: none"> Not superior to clopidogrel for reducing cardiovascular events in PAD. 	Similar rates of major bleeding compared to clopidogrel.
Vorapaxar	TRA 2°P-TIMI ^{45,46}	<ul style="list-style-type: none"> Reduction of stroke, MI, or CV death when added to standard of care for atherosclerosis. Reduction in ALI and peripheral revascularization in PAD. 	Increased risk of moderate or severe bleeding and intracranial hemorrhage compared to standard of care.
Rivaroxaban	COMPASS ^{16,34} VOYAGER PAD ⁴⁷	<ul style="list-style-type: none"> Reduction in stroke, MI, or cardiovascular death and reduced adverse limb events when added to aspirin. Following revascularization, reduced amputation, stroke, MI, or CV death when added to aspirin. 	Increased rates of major bleeding compared to aspirin.

ommended for primary prevention of CV events, though the use of aspirin may be considered for early-onset PAD (< 50 years of age).^{29,42,43} Notably, early-onset PAD is rare and not currently extensively characterized.

Ticagrelor vs clopidogrel. In the EUCLID trial, patients with PAD who had an ABI of ≤ 0.80 or previous lower-limb revascularization were randomly assigned to receive ticagrelor or clopidogrel.¹² The primary efficacy endpoint (CV death, MI, or ischemic stroke) occurred in 10.8% of patients receiving ticagrelor and 10.6% of patients receiving clopidogrel. There were no differences observed in ALI or major bleeding between the 2 groups. The authors concluded that ticagrelor was not superior to clopidogrel for CV event reduction in PAD. Notably, ticagrelor does not currently have an indication for use in PAD.⁴⁴

Vorapaxar. Vorapaxar was compared to a placebo in a randomized trial called TRA 2°P-TIMI in patients with a history of atherosclerosis, including PAD.⁴⁵ The primary endpoint was a composite of stroke, MI, or CV death. After 3 years, 9.3% of patients in the vorapaxar group and 10.5% of patients in the placebo group experienced stroke, MI, or CV death ($P < .001$). Moderate or severe bleeding and intracranial hemorrhage were significantly more likely in the vorapaxar group. After 2 years, the data and safety board advised discontinuation of the study in patients with a history of stroke due to the increased risk of intracranial hemorrhage.

A subsequent analysis of the TRA 2°P-TIMI trial evaluated the subgroup of patients with PAD.⁴⁶ There was no reduction in stroke, MI, or CV death with vorapaxar in this analysis, but there was a significant decrease in ALI and peripheral revascularization with vorapaxar. An increased bleeding risk with vorapaxar was also observed.

Aspirin plus low-dose rivaroxaban. The COMPASS study investigated rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg daily, and aspirin 100 mg daily in patients with PAD of the lower extremities.^{16,34} The major finding of this randomized trial was a reduction in stroke, MI, or CV death with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily (5% vs 7%; $P = .0047$) and a reduction in MALE (1% vs 2%; $P = .0037$) compared to aspirin 100 mg daily. This outcome was also consistent in patients with higher-risk features, such as smoking, T2D, or chronic kidney disease. Major bleeding rates were increased with the rivaroxaban group (3% vs 2%; $P = .0089$).

In the VOYAGER PAD study, patients with PAD who had previously undergone revascularization received rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.⁴⁷ During randomization, patients were stratified according to clopidogrel use to reduce confounding of results due to concomitant P2Y₁₂ therapy. Patients in the rivaroxaban group had a reduced rate of amputation for vascular causes, ischemic stroke, MI, or CV death (17.3%) vs the aspirin only group (19.9%; $P = .009$). Major bleeding was more common in the rivaroxaban group via thrombolysis in myocardial infarction (TIMI) and International Society on Thrombosis and Haemostasis (ISTH) definitions, but only the ISTH bleeding was statistically significant. Intracranial hemorrhage occurred at a similar rate in both groups.

Revascularization

Outcomes following revascularization for treatment of lower-extremity disease in PAD are not clearly characterized, and patients should be carefully selected for these procedures.⁴⁸

In particular, patients should have trialed GDMT, including a structured exercise program for at least 3 months. Additionally, the occlusion should have certain characteristics and locations in arterial vessels, the details of which are beyond the scope of this discussion.

An analysis of lower-extremity revascularization in patients from the EUCLID trial demonstrated that there was a higher risk for MACE and limb ischemia in patients undergoing post-randomization lower extremity revascularization.⁴⁹

SUMMARY

PAD is an often underdiagnosed and undertreated disease with significant risk for CV and limb complications. Prompt diagnosis and initiation of GDMT can help reduce the risk of complications from the disease, reduce claudication symptoms, and improve functional capacity. Atherothrombotic events lead to significant morbidity in PAD, and accurately selecting effective treatment to prevent thrombosis is essential for clinicians to ensure optimal patient outcomes. ●

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